Lyme Disease… Challenging Disease… Challenging Vaccine

LTC Bryan L. Martin
FAAAI, FACAI, FACP
Assistant Chief
Allergy-Immunology Department

Lyme Disease

- Most common tick-borne disease in the US and Europe
- 1975: First identified in US, after outbreak of arthritis near Lyme, Connecticut
- 1982: Burgdorfer identifies spirochetes in midgut of adult deer tick
- December 1998: LYMErix Vaccine approved

Lyme Disease

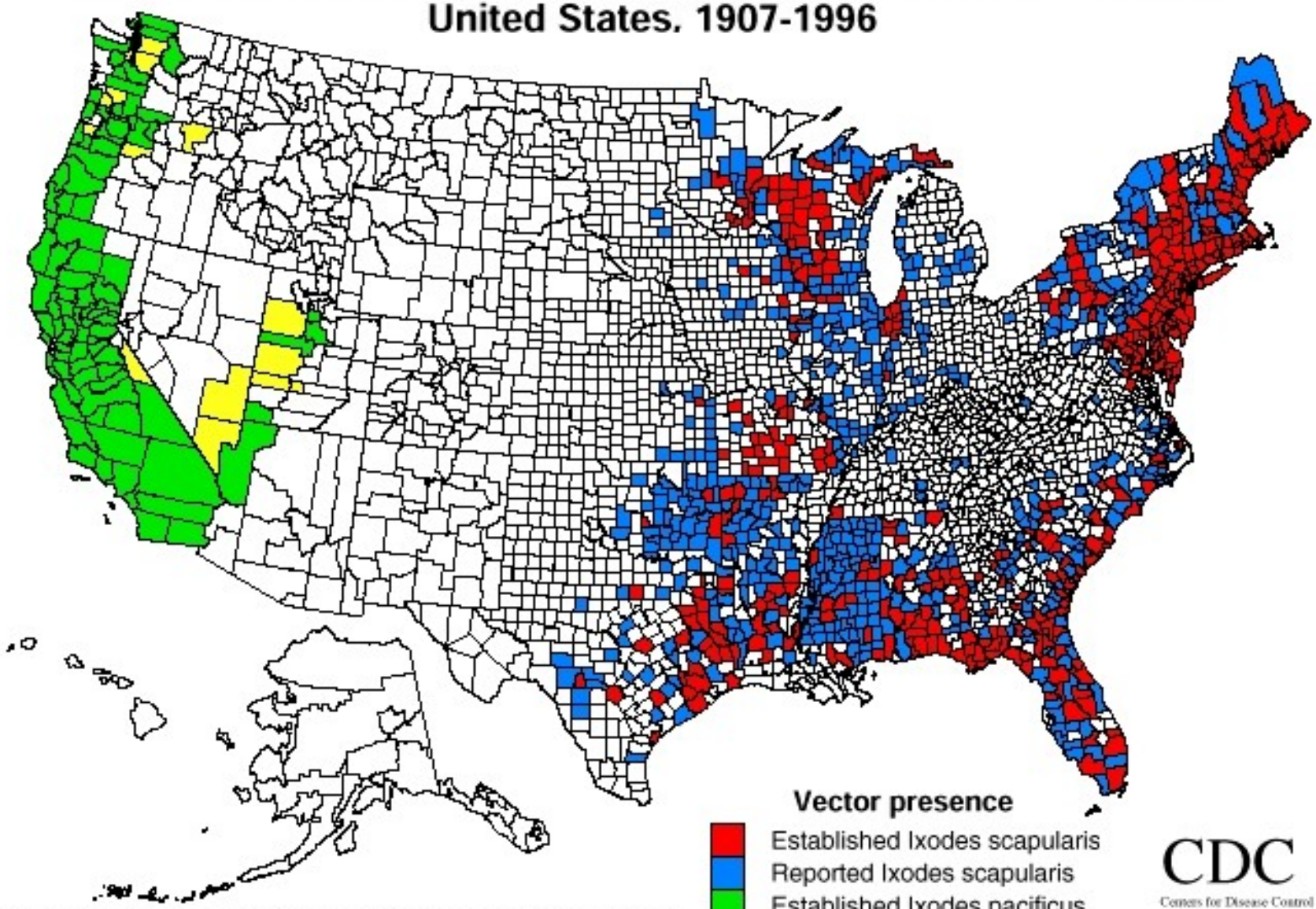
- Causative agent
  - Tick borne spirochete
  - *US*
    - *Borrelia burgdorferi*
  - *Europe*
    - *B. garinii*
    - *B. afzelii*

Ixodes sp.

- Deer tick
  - feeds on white tailed deer, white footed mouse, other mammals and birds

* Ixodes ricinus complex: I. Scapularis (deer tick also transmits ehrlichiosis, babesiosis); I. pacificus

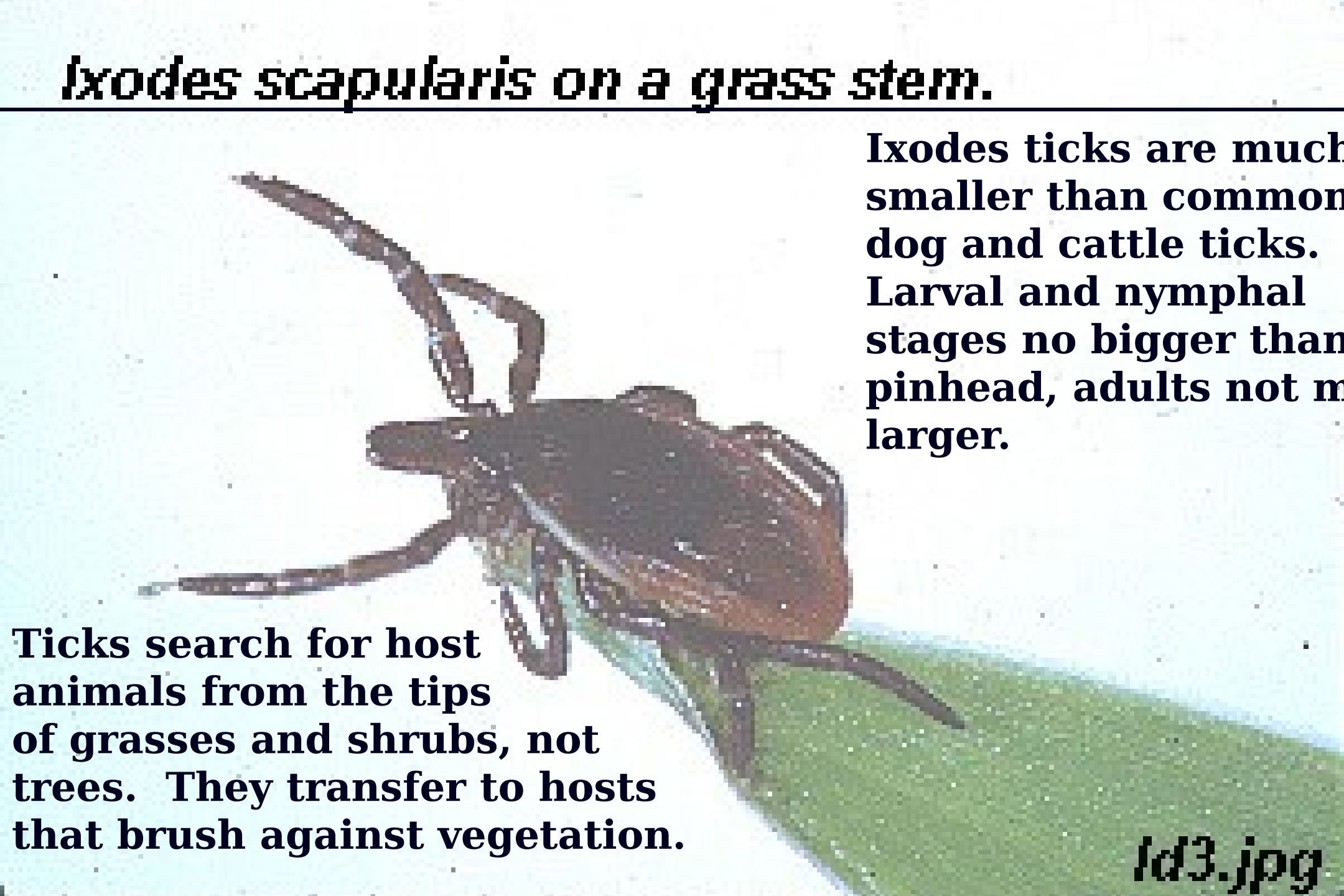
Established* and reported** distribution of the Lyme disease vectors Ixodes scapularis (I. dammini) and Ixodes pacificus, by county, United States. 1907-1996



*at least 6 ticks or 2 life stages (larvae, nymphs, adults) identified.
**at least 1 tick identified.

CDC
Centers for Disease Control and Prevention

Ixodes scapularis on a grass stem.

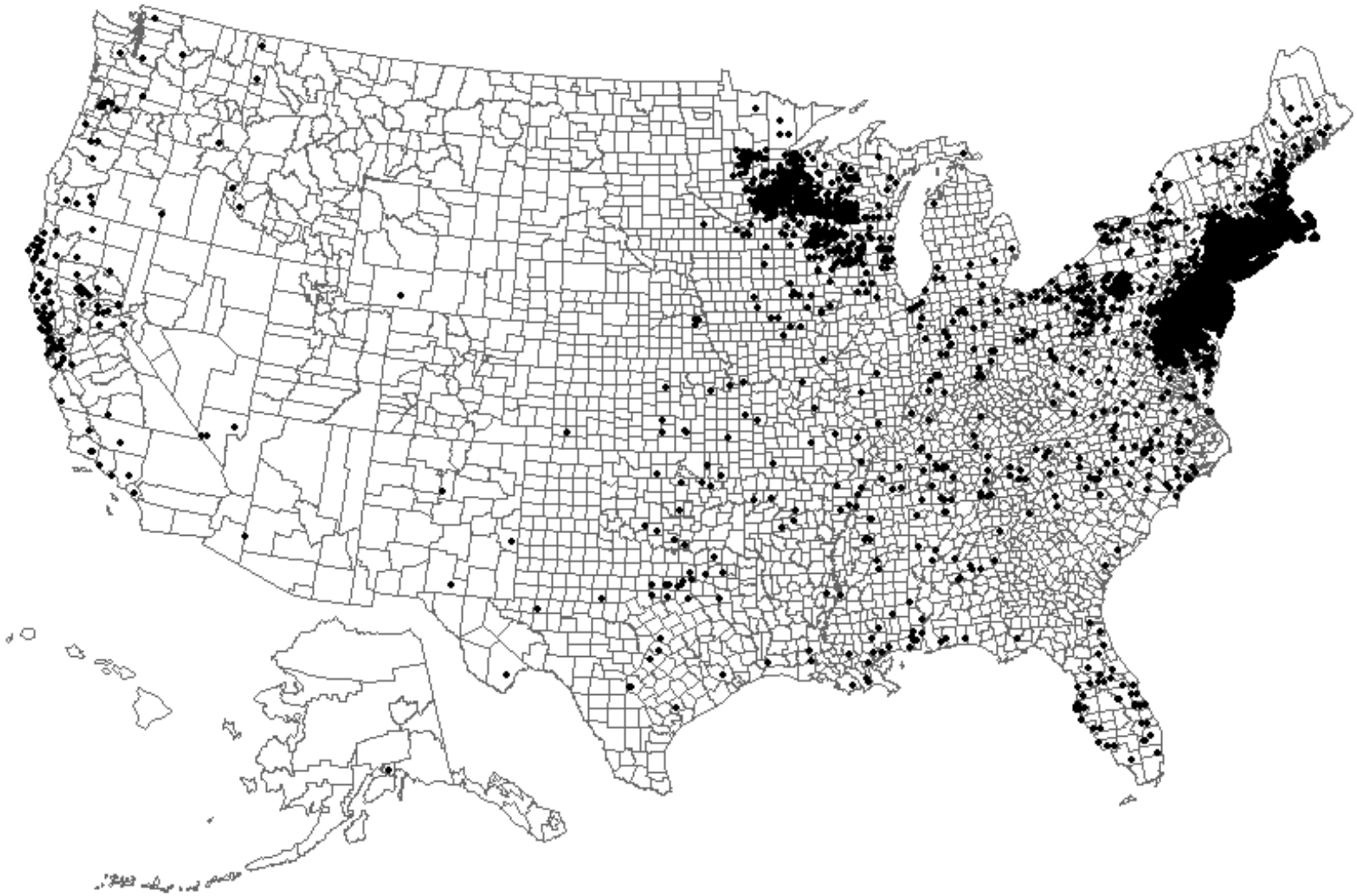


Ixodes ticks are much smaller than common dog and cattle ticks. Larval and nymphal stages no bigger than pinhead, adults not m larger.

Ticks search for host animals from the tips of grasses and shrubs, not trees. They transfer to hosts that brush against vegetation.

id3.jpg

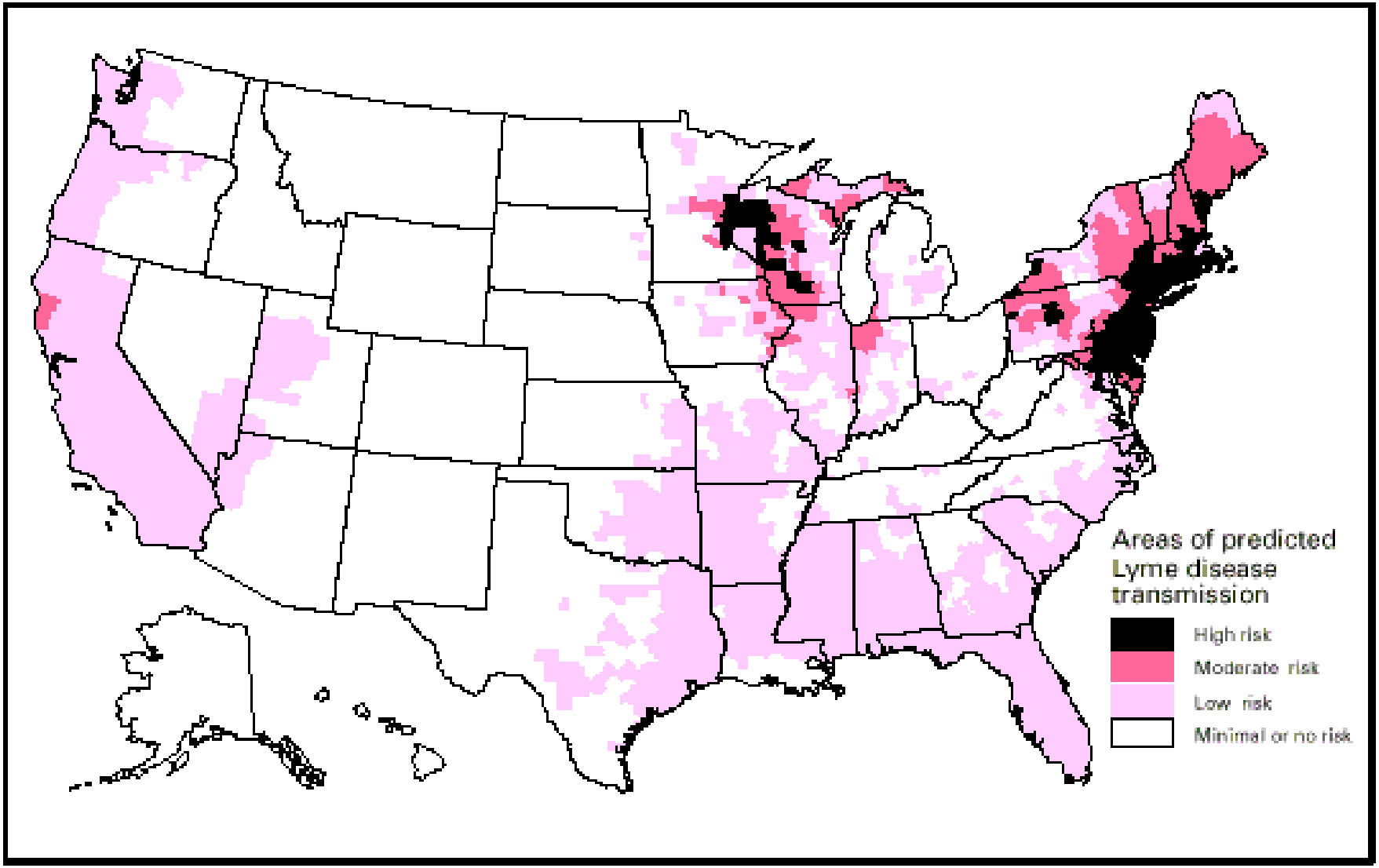
Reported Cases of Lyme Disease, United States, 1998*



*1 dot = 1 case, randomly placed within county of residence; 16,801 cases

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

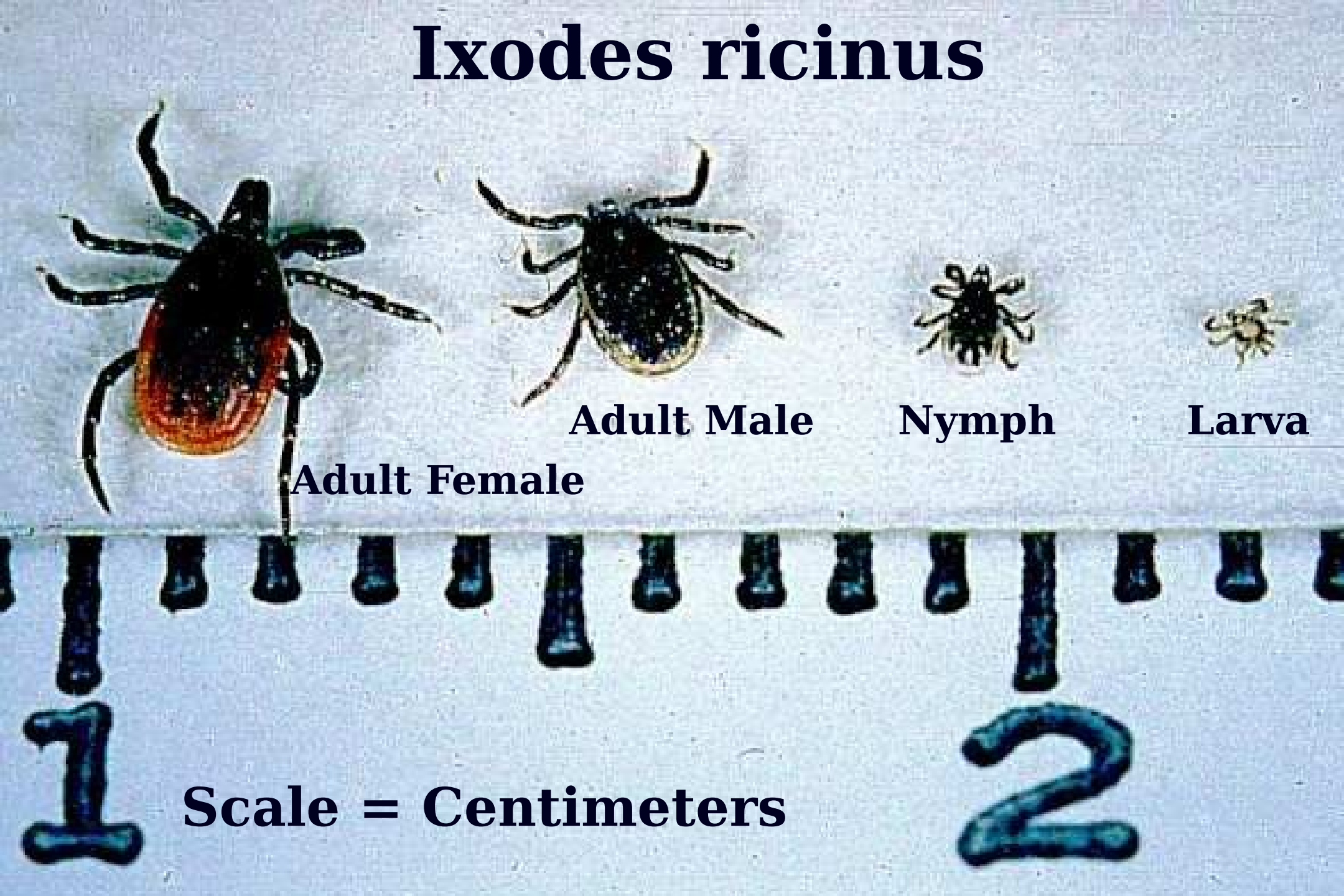
National Lyme disease risk map with four categories of risk



Note: This map demonstrates an approximate distribution of predicted Lyme disease risk in the United States. The true relative risk in any given county compared with other counties might differ from that shown here and might change from year to year. Risk categories are defined in the accompanying text. Information on risk distribution within states and counties is best obtained from state and local public health authorities.

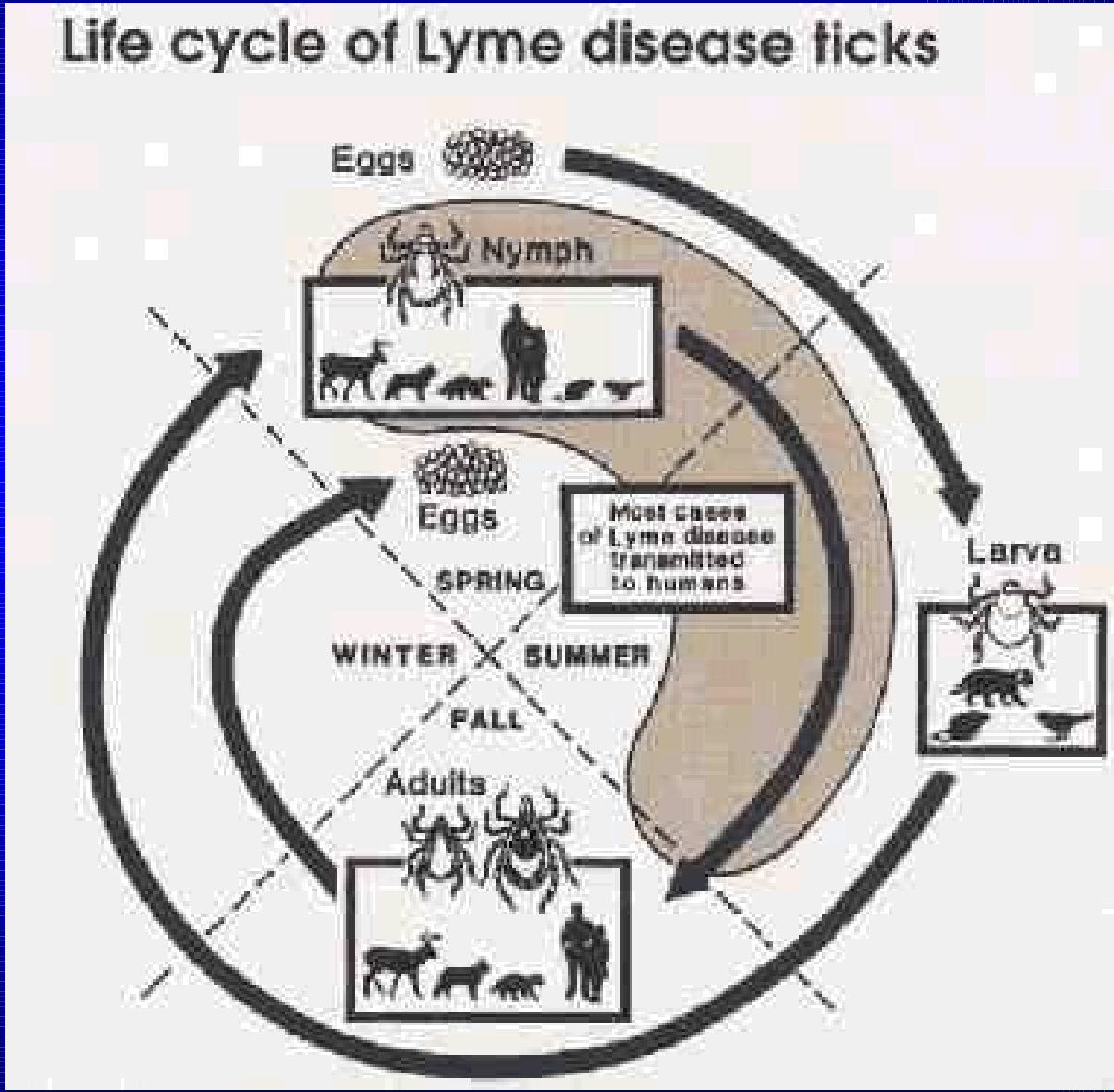
World Wide Distribution: Lyme Dis

Ixodes ricinus



2 year tick life cycle

- Summer 1: Eggs hatch into larvae, feed on small mammals & birds
- Fall 1: become inactive
- Spring 2: molt into nymphs
- Fall 2: molt into adults, feed and mate on large animals, females drop off to lay eggs on ground



Lyme Disease

- Transmission requires 36+ hours of attachment
  - Slow feeders, meal can take several days
- Typically nymph stage transmits disease to humans
  - Small size, ability to feed for ample time
  - Larvae rarely carry the infection
  - Adults more likely to be found, more active in cooler months
- 1993-97: 12,451 cases annually to CDC (25-fold increase since 1982)
- NE, mid-Atlantic, upper north central regions, NW California areas (Note: **endemic in MD not VA**)

Clinical Lyme Disease: Early S/S

- Asymptomatic infection is possible
- Incubation is typically 7-14 days, but may be 3-30 days
  - Fatigue
  - Chills and fever
  - Headache
  - Muscle and joint pain
  - Swollen lymph nodes
  - Erythema Migrans

Erythema migrans

- Site of bite
- 3 days to 1 month after bite
- Expands, often to large size
- Center may clear as it enlarges, leading to bulls-eye appearance
- Not typically painful

Lyme Disease: Late Phases

- Arthritis
  - Usually in one or more large joints, especially knees
  - Likely to present as brief bouts of pain and swelling
- Nervous System
  - Numbness, pain, Bell's palsy
  - Meningitis, headache
- Cardiac (rare)
  - Arrhythmias (a-v block)
  - Myocarditis
- Rare deaths reported

Lyme Disease Diagnosis

- Early identification of tick bite, history of prolonged exposure (> 24 hours), clinical symptoms - early treatment best
- Serologies can be helpful: ELISA or IFA then more specific Western immunoblot pattern
- Not all patients have early classic symptoms
- Repeated infection is possible

Lyme Disease: Public Perception of Risk

- Most commonly diagnosed vector-borne disease
- Reports from 48 states, increasing number
- 1992-97: > 62,000 cases reported
- Underreporting & over-diagnosis common
- Deer tick is smaller than a sesame seed therefore the validity of tick removal strategies unclear
- High public awareness & fear of disease
- High consumer interest in vaccine

Lyme Diseases
Personal protection from tick bites

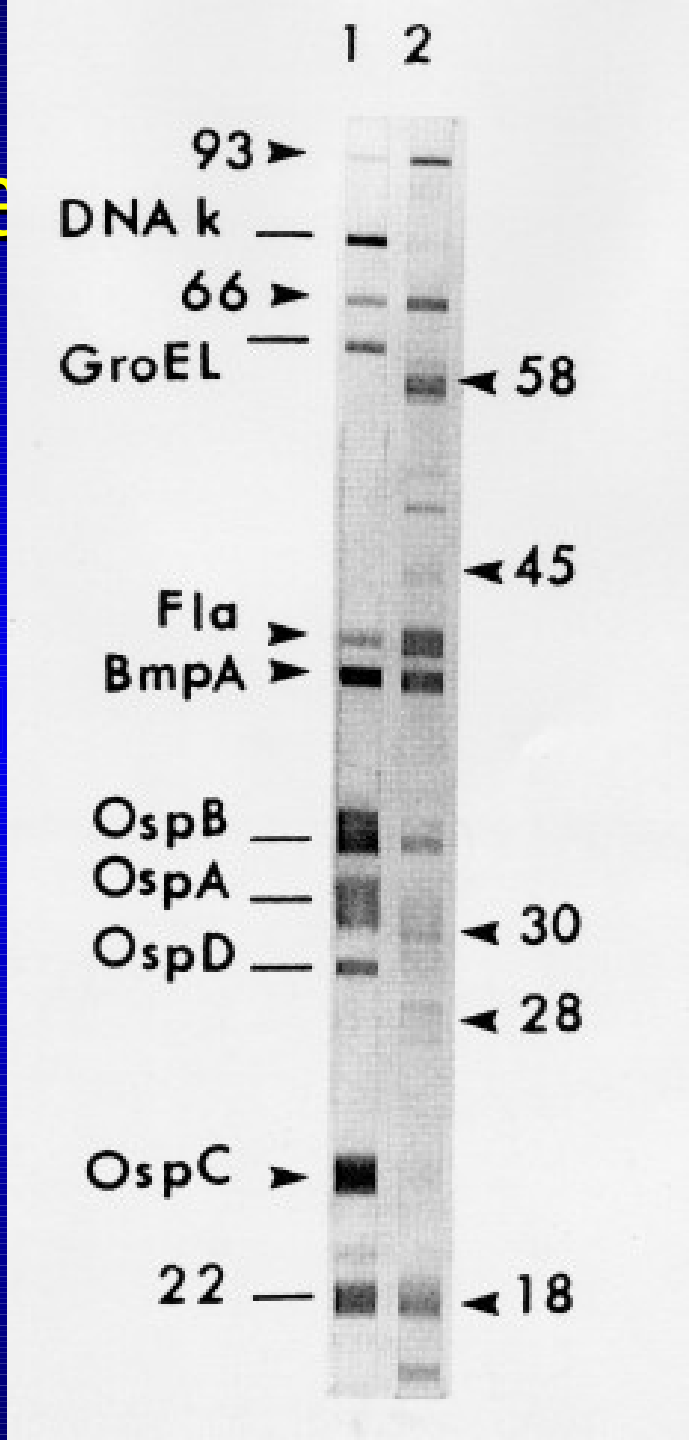
- Avoid known tick-infested areas
- Wear light colored clothing; ticks are easily spotted
- Tuck pant legs into socks
- Tape area where pants and sock meet
- Spray DEET insect repellent on clothes and skin
- Wear hat, long sleeved shirt
- Walk in center of trails, avoid overhanging grass
- Remove ticks as soon as possible

Lyme Diseases: Treatment

- Antibiotics
  - After tick bite without known infection: probably not warranted
  - Effective in early Lyme
  - Somewhat effective in Late stages of Lyme

Lyme Vaccine Strate

- Outer membrane of B. burgdorferi unique: genes encoding its proteins are extrachromasomal located on linear plasmids
- 3 major immunogenic Outer-surface proteins
  - Osp-A (30 kDa)
  - Osp-B (34 kDa)
  - Osp-C (23 kDa)



Lyme Vaccine

- Recombinant outer-surface protein A (rOspA)
  - LYMErix™ SmithKline Beecham Pharm
    - 0.5 ml dose = 30 μg purified rOspA (from *E. coli* expression vector), AlOH adjuvant
    - No thimerosal preservative
- Age: 15 to 70 (pediatric studies in progress)
- Dose @ 0, 1 & 12 months with annual booster
  - Timing: best to start Jan-Feb for April season
- ImuLyme by Pasteur Merieux Connaught in phase III trials is also against Osp-A

MMWR Vol 48(RR07); 4 Jun 99: 1-18 or

Antigenic Shift

- Spirochetes residing in the tick gut at initiation of blood meal express primarily Osp-A
- Feeding begins: Osp-C expression increases, Osp-A expression decreases
- Spirochetes reaching mammalian host pass through tick salivary glands: by this time they express primarily Osp-C
- WHY use anti Osp-A?
  - Less variability than Osp B, C or D

Lyme Disease Vaccine: Unique Mechanism of Action

Prevention of Transmission of Spirochete rather than neutralization of host-infection

- Vaccinee anti-rOspA antibody enters tick gut
- Ab's kill *B. burgdorferi* (Bb) in the midgut of the tick, preventing transmission & infection
- Possible because it generally takes 24-48 hours of feeding before the tick transmits Bb
- Antigen (OspA) expressed primarily by spirochete in tick gut

Lyme Vaccine Indications - 1

Question: Who should receive this vaccine?

NOT recommended by AFEB as a routine military vaccine requirement (May 1999)

- Tick-borne disease frequency low at training sites
- Rate of tick infection from surveillance program relatively low
- Elective vaccine for those at greatest risk
- No data about safety with multiple other vaccines

Lyme Disease Prevention

Healthy People 2010 Goals: DHHS

- Includes recommendation for 60% reduction in Lyme disease by 2010
- Concerns raised about effectiveness of avoidance measures alone since the tick is VERY small & easily overlooked
- **High risk personnel**: occupation, geography, leisure, special military settings?

Lyme Vaccine Indications - 2

Decision to administer Lyme vaccine:

"individual risk, which depends on a person's likelihood of being bitten by an infected tick vector"

- Geographic distribution of risk (varies between states, within counties & townships)
- Assess person's activities: recreational, property maintenance, occupational, leisure pursuits
- Ability to seek medical care & avoid prolonged tick exposure (removal of tick in less than 24 hours)
- Probability of completing vaccine series

Lyme Vaccine Indications - 3

Highest potential benefit for

- Persons who reside, work or recreate in areas of high or moderate risk “frequent or prolonged contact”
- Persons unlikely to practice careful tick bite precautions or unlikely to access care
- Travelers are considered at lesser risk than persons who reside, work or recreate regularly in areas of high or moderate risk (efficacy NOT proven for Eurasian strains)

Lyme Vaccine Indications - 4

High risk personnel for Lyme disease:

- Prior Lyme disease (natural immunity unreliable)

Currently NOT indicated for

- Children < 15 years & persons > 70 years
- Pregnant women: register women who receive vaccine accidentally (1-800-366-8900)
- Treatment resistant Lyme arthritis, chronic joint &/or neurologic disease, AV block (2nd/3rd)
- Those whose exposure is minimal or none

Lyme Disease Vaccine: Questions

Are there unknown vaccine risks for certain subpopulations?

- Chronic, poorly responsive Lyme arthritis
  - associated with certain class II MHC (DR4)
    - high levels of Ab to OspA (C-terminal epitope) correlate with severity & duration of arthritis
    - mechanism proposed: molecular mimicry between dominant T-cell epitope of OspA & human leukocyte function associated antigen 1

Infect Immun 1999;67:173-81; Science 1998;281:703-6; Infect Immun 1993;61:2774-9.

Lyme Vaccine Side Effects in 10,936 (ACIP review MMWR 4Jun99;48:1-17)

- Soreness at the injection site: 24%
  - AlOH containing placebo: 7.6%
- Redness, swelling more frequent than placebo but less than 2% ($p < 0.001$)
- Myalgias, influenza-like illness, fever, chills:
  - < 3.2% (more common than placebo)
- Arthralgia, myalgia within 30 days ($p < 0.05$)
- No data about annual booster doses

31 sites, randomized trial: NEJM 1998;339:209-15 - passive surveillance

ACIP: Advisory Committee on Immunization Practices

Adverse Reaction Rates with Lyme Vaccine: Overall for Dose 1, 2 & 3

Side Effects:	< 30 Days	> 30 Days
Injection Site Soreness	93%	NA
Redness, swelling	41%/30%	NA
Arthralgias, stiffness	25%	14%
Fever/chills	3.5%	3%
Headaches	38%	5%

Lyme Vaccine: Early Unsolicited AE's
% Receiving 2nd Dose, % Recurrence

Symptom	Vac1 N=	Vac2 %	Recur %	Plac1 N=	Plac2 %	Recur %
Inj Site Pain	1189	96%	25%	376	94%	19%
Inj Site Swelling	44	84%	8%	10	80%	0%
Fatigue	114	91%	11%	101	88%	8%
Fever	98	83%	3.7%	42	90%	0%
Flu-like Sxs	99	87%	8%	53	81%	7%
Arthralgias**	194	81%	13%	176	76%	3.8%
Myalgia	160	85%	5.9%	90	83%	2.7%
Headache	149	89%	12%	125	90%	8%
Rash	30	90%	3.7%	24	100%	4.2%
Achiness	101	86%	8%	69	85%	3.4%

Efficacy of LYMErix™

Efficacy using an intention-to-treat analysis:

- After 2 doses: 49% [CI 15-69%]
- After 3 doses: 76% [CI 58-86%]

Efficacy in protecting against asymptomatic infection (no sxs, WB seroconversion Yr 1&2)

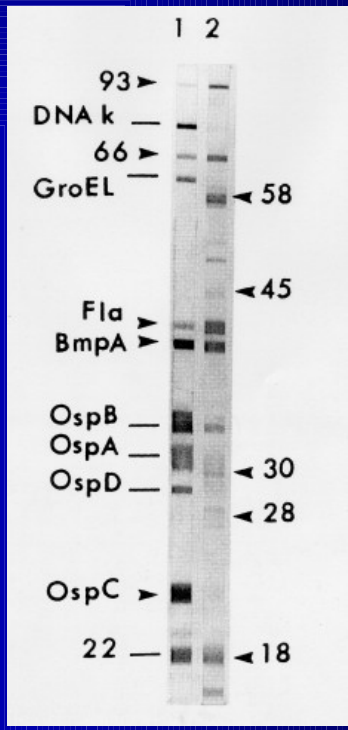
- 83% [CI 32 - 97%] in year 1
- 100% [CI 26 - 100%] in year 2

Need for annual boosters: How many, how long?

- No data, but titers decline rapidly

Steere AC, Sikand VK et al. NEJM 1998;339:209-15

Effects on Dx or Rx of Lyme Disease



LYMErix™ (rOspA) may

- Induce a false positive ELISA for Lyme
- Induce a 31 kD Western blot (WB) band

LYMErix™ does not:

- Mask, attenuate or alter clinical presentation
- Affect duration of symptoms following Rx
- Interfere with determination of WB positivity as defined by CDC banding pattern criteria

Lyme Vaccine: Challenges

- Complexity of informed consent
- Poor vaccine efficacy if series NOT completed
  - Patient compliance monitoring & FU provided by SK
    - Free tracking system by Manufacturer
    - Data suggests > 85% complete series (highly motivated population)
- Not required but Healthy 2010 Goals include reduction of Lyme by > 66%

Lyme Disease Vaccine: Cost

- No bulk purchase centrally to assist MTF's
- Demand in view of aggressive advertising & public awareness of disease risk
- If the demand exceeds 25% of eligible population, could add significantly to cost of pharmacy
- Should we restrict sites where it is given?
- TRICARE: not a defined benefit